

## Alcohol effect on GPe connectivity

Using seed-to-voxel (i.e. whole brain) connectivity analyses - with GPe as seed region - provided the following significant results. Alcohol directly affected the GPe activity demonstrated by the shifting of the time series of the BOLD signal (Supplementary Figure 1A). See Supplementary Table 1 and Supplementary Figure 1B for seed-to-voxel connectivity results. These results are reported at a voxel-height threshold of  $p < 0.001$  and an extent threshold of  $p < .05$  FDR corrected for multiple comparisons.

### Right GPe connectivity changes

The seed-to-voxel functional connectivity revealed significant decreases in connectivity between the right GPe seed and the bilateral NAcc, bilateral putamen, subgenual anterior cingulate (ACC), bilateral caudate, and left orbitofrontal cortex (OFC) following IV alcohol infusion. Additional regions that significantly showed decreased connectivity were in the left cerebellum, right frontal pole and right middle frontal gyrus. We observed a significant alcohol-induced increase in connectivity between the right GPe seed and the right precentral gyrus, areas within the frontal pole, left OFC, inferior frontal gyrus (pars triangularis), left middle/superior temporal gyri (posterior portion), left occipital fusiform gyrus, and lateral occipital cortex (inferior division).

### Left GPe connectivity changes

Reduced connectivity after alcohol infusion with the left GPe was detected in areas of the bilateral thalamus, bilateral caudate, right pallidum, and the left NAcc, putamen, and subgenual ACC/OFC. We also found significantly reduced left GPe connectivity with subregions of the frontal cortex (middle/superior gyri, right frontal pole, right central operculum, left precentral gyrus), cerebellum, precuneus, temporal cortex (left middle/superior gyri, left temporal pole, Heschl's gyrus), left angular gyrus, and left superior lateral occipital cortex. Alcohol-induced increases in connectivity with the left GPe were found in the bilateral paracingulate, medial frontal and superior frontal gyri, frontal pole, and insular cortices.

## Supplementary discussion

We aimed to translate the preclinical finding from Abrahao et al. (2017) through an IV alcohol infusion paradigm. We measured resting-state functional connectivity in “sober” (i.e., BAC = 0.00 g/dl) and “binge drinking” (i.e., BAC = 0.08 g/dl) states. We did see functional connectivity between the right GPe and striatum regions decrease bilaterally in the “binge drinking” state, consistent with the rodent model. Given the theorized role of the GPe as part of the arkypallidal pathway, alcohol can be interpreted here as disrupting the ability of the GPe to send signals to stop or pause before actions [2].

In addition to the hypothesized dorsal striatum regions (i.e., caudate, putamen), we saw that alcohol reduced connectivity between the GPe and the ventral striatum (i.e., NAcc). This was unexpected given the lack of evidence for direct structural connectivity between these regions. However, there are several methodologic differences between work in animal and human models that may explain this finding. First, BOLD signal has low resolution in comparison to patch-clamp recordings. Electrophysiology has been used to validate the basal ganglia circuitry within a BOLD connectivity context using an optogenetic-resting state fMRI method [3], but given the GPe has common projections to the subthalamic nucleus with the ventral pallidum [4, 5], which we would expect to functionally connect with the NAcc, it is possible that connectivity signal from that region is confounding the GPe connectivity signal in this study. Moreover, resting state functional connectivity is an indirect measure of pathway communication and is unable to use timing to establish directionality. Thus, it is possible this finding may reflect indirect connectivity, such as through the ventral tegmental area [6].

We also unexpectedly found that alcohol infusion decreased connectivity between GPe and cerebellar / frontal pole areas, and increased connectivity between GPe and PFC / temporal gyri. These are not regions found to be directly connected to the GPe and involved in stop-signaling. However, as highlighted in the previous paragraph, these findings may reflect indirect connectivity. For example, cerebellar regions are connected to the CM/Pf complex of the thalamus [7], which is thought to be affected by GPe activity [5]. Our finding that alcohol increased connectivity between GPe and PFC/temporal areas is particularly unexpected. However, previous studies have shown that substance dependent individuals have increased connectivity during rest in executive control networks [8] and between NAcc and dlPFC regions [9]. Given that resting state is typically associated with reduced executive control function, this increased coupling between GPe and lateral PFC activity may reflect impaired functioning. One possible mechanism underlying this finding could be that alcohol is impacting the function of long-range GABAergic projections between the GPe and frontal gyrus [10].

Our connectivity findings followed a somewhat lateralized pattern, where connections to left side regions from both right and left GPe increased with alcohol administration and connections to right side regions decreased. Alcohol has previously been shown to reduce the lateralization of specific functions, particularly in terms of greater left lateral increases and right lateral decreases in connectivity at rest [11]. The greater left-side increases in connectivity (both from ipsi- and contralateral GPe regions) may reflect this pattern as well. We would point out that there were mostly contralateral alcohol-decreases in connectivity from the left GPe, suggesting reductions in connectivity on the right side. We would also point out from the perspective of the role of the GPe pathways, previous work finds that connectivity strength in right-lateralized hyperdirect and indirect basal ganglia/frontal pathways predicted successful response inhibition (Jahfari et al., 2011). On the other hand, increases in left ipsilateral connectivity in individuals with chronic alcohol use has been associated with

compensatory function [12]. Taken together, the lateralization pattern may reflect alcohol related impairment of standard inhibitory pathways and increases in “alternative” neural communication routes.

## Supplementary References

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